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REVIEW

# Comprehensive treatment for the peritoneal metastasis from gastric cancer

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## Abstract

Recently, a novel comprehensive treatment consisting of cytoreductive surgery (CRS) and perioperative chemotherapy (POC) was developed for the treatment of peritoneal metastasis (PM) with a curative intent. In the treatment, the macroscopic disease is completely removed by the peritonectomy techniques in combination with POC. This article reviews the results of the comprehensive treatment for PM from gastric cancer, and verifies the effects of CRS and POC, including neoadjuvant chemotherapy (NAC) and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Completeness of cytoreduction, peritoneal carcinomatosis index (PCI) less than the threshold levels after NAC,

absence of ascites, cytologic status, pathologic response after NAC are the independent prognostic factors. Among these prognostic factors, PCI threshold level is the most valuable independent prognostic factor. After staging laparoscopy, patients with PM from gastric cancer are recommended to treat with NAC before CRS. After NAC, indication for CRS is determined by laparoscopy. The indications of the comprehensive treatment are patients with PCI less than the threshold levels, negative cytology, and responders after NAC. Patients satisfy these factors are the candidates for the CRS and HIPEC.

**Key words:** Gastric cancer; Hyperthermic intraoperative intraperitoneal chemotherapy; Peritoneal metastasis; Peritonectomy



**Core tip:** This article reviews the results of the comprehensive treatment for peritoneal metastasis from gastric cancer, and verifies the effects of cytoreductive surgery and perioperative chemotherapy, including neoadjuvant chemotherapy (NAC), and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Multivariate analyses revealed that the completeness of cytoreduction, peritoneal cancer index less than the threshold levels after NAC, cytologic status, pathologic response after NAC are the independent prognostic factors. Patients satisfying these factors are recommended to undergo D2-gastrectomy combined with complete removal of PC and HIPEC.

Yonemura Y, Canbay E, Endou Y, Ishibashi H, Mizumoto A, Li Y, Liu Y, Takeshita K, Ichinose M, Takao N, Saitou T, Noguchi K, Hirano M, Glehen O, Brűcher B, Sugarbaker PH. Comprehensive treatment for the peritoneal metastasis from gastric cancer. *World J Surg Proced* 2015; 5(2): 187-197 Available from: URL: http://www.wjgnet.com/2219-2832/full/v5/i2/187.htm DOI: http://dx.doi.org/10.5412/wjsp.v5.i2.187

## INTRODUCTION

Peritoneal metastasis (PM) was considered as a terminal stage with very poor prognosis. In the late 1990s, Peritoneal Surface Malignancy Oncology Group International proposed a novel comprehensive treatment consisting of cytoreductive surgery (CRS) and perioperative chemotherapy (POC). In the comprehensive treatment, the macroscopic disease is completely removed by the peritonectomy techniques in combination with POC. POC includes neoadjuvant intraperitoneal/systemic chemotherapy (NIPS), bidirectional intraperitoneal and systemic induction chemotherapy (BISIC), laparoscopic hyperthermic intraperitoneal chemotherapy (LHIPEC), hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC), extensive intraoperative peritoneal lavage (EIPL), early postoperative intraperitoneal chemotherapy and late postoperative systemic chemotherapy[1-3].

This article reviews the rationale of the comprehensive treatment for PM from gastric cancer.

### *Quantitative evaluation of PM*

Preoperative and intraoperative diagnosis for PM should provide reliable information about the tumor burden and distribution of PM[4,5]. At present, the peritoneal carcinomatosis index (PCI) is used worldwide[5]. The abdominal compartments were divided into 13 sectors. The tumor involvement in each compartment is macroscopically evaluated by the lesion size scores from 0 to 3. PCI described the tumor load in the abdominal cavity from 0 to 39. PCI score is considered an important prognostic indicator after CRS. Threshold levels of PCI for favorable *vs* poor prognosis were reported from several high volume centers. Glehen *et al*[6,7] reported that all patients died within 3 years after CRS when the PCI score was higher than 12. Even if complete cytoreduction appears to be possible, patients with PCI of higher than 12 should be contraindicated for the aggressive CRS[7]. Yonemura *et al*[8] reported patients with PCI of lower than 6 survived significantly better than those with PCI of higher than 7. Yang *et al*[9] proposed the best candidates for the CRS could be patients with PCI < 20. To select patients for CRS, PCI assessed by preoperative computed tomography (CT) may have an important role. However, the accuracy of CT for the preoperative evaluation of PM from gastric cancer is limited, because the size of PM from gastric cancer is usually small[10].

In the preoperative evaluation for PM, Hong *et al*[11] proposed a new classification consisting of three grades. Grade 0 was defined as PM detected during operation with no evidence of PC in the preoperative evaluation, and grade 1 was defined as PM or ascites detected by CT scan, however, no bowel involvement or need for paracentesis was recorded. Grade 2 was defined as bowel wall involvement or a large amount of ascites requiring paracentesis[11]. When the grade 0 and grade 1 were summed as low-grade and grade 2 was defined as high-grade, survival of patients with low-grade PM was significantly longer than the patients with high-grade PM. Among the patients with low-grade PC, patients who received a gastrectomy had longer survival than those who did not receive a gastrectomy[11]. This staging system is useful to determine the indication of gastrectomy or systemic chemotherapy.

In the Japanese general rules of gastric cancer treatment, status of PM is grouped into three categories: P0/Cy0, Po/Cy1, and P1[12]. P0/Cy0 status is no macroscopic PM and a negative peritoneal wash cytology. P0/Cy1 status shows no macroscopic PM but positive peritoneal wash cytology, and P1 status means the macroscopic PM with or without a positive peritoneal cytology. The survival of patients with P0/Cy1 is similar to that of patients with P1[13,14]. The proliferative activities of peritoneal free cancer cells (PFCCs) is considered

high[14]. Accordingly P0/Cy1 status is classified into stage Ⅳ disease even in patients with no macroscopic PM. Bando *et al*[13] reported that 114 (11%) of 1039 potentially curable patients showed positive cytology (P0/Cy1).

However, there is no universal consensus on the most appropriate treatment regimen for this particular group of patients. Cabalag *et al*[15] performed a meta-analysis of treatment results in patients with P0Cy1 status. The use of S1 monotherapy was associated with a significant survival benefit[16]. A recent randomized controlled trial examining EIPL with intraperitoneal chemotherapy (IPC) showed a significant improvement on overall survival (5-year overall survival, 43.8% for EIPL plus IPC group compared with 4.6% for IPC group)[17]. In addition, the role of gastrectomy remains unclear in patients with P0/Cy1[18]. Furthermore, Kang *et al*[19] reported that peritoneal washing cytology was not able to predict peritoneal recurrence or survival in gastric cancer patients[19]. These results indicate that more clinical trials should be done to define the best treatment option for patients in P0/Cy1 status.

### *Score of the completeness of cytoreduction*

Score of the completeness of cytoreduction score (CC score) is an assessment grade after CRS[4]. The residual disease after CRS is classified into four grades of CC-0 to CC-3. CC-0 indicates a status of no macroscopic residual tumors after CRS. CC-1 means residual tumor burden of less than 2.5 mm in diameter. CC-2 shows that the total tumors between 2.5 mm and 25 mm in diameter are left. CC-3 means the residual tumor of greater than 25 mm in diameter. The CC-1, CC-2 and CC-3 are evaluated as the incomplete cytoreduction. Histological positive margin is classified CC-1[2].

### *The role of CRS in the comprehensive treatment*

CRS or chemotherapy alone can not confer the cure for patients with PM. In contrast, CRS combined with intraperitoneal chemotherapy applications improves a long-term survival, because invisible metastasis left after CRS can be eradicated by intraperitoneal chemotherapy[3]. Accordingly, the comprehensive treatment is now justified a state-of-the-art treatment for patients with PM.

Among the treatment options using in the comprehensive treatment, the completeness of CRS is the important prognostic factor[8,20]. Survival of patients underwent incomplete cytoreduction was not improved, as compared with that of patients treated with chemotherapy alone[2]. In contrast, patients underwent complete cytoreduction survived significantly longer than those treated with incomplete cytoreduction or chemotherapy alone. PCI score correlates with the completeness of cytoreduction. CC0 was achieved in 91% of the patients when the PCI score was lower than 6, but in only 42% of the patients with a PCI $\geqslant$ 7[8]. Even in patients with complete cytoreduction, all patients with PCI higher than the threshold value died of the recurrence[7,8]. Accordingly, surgeons should decide to perform CRS for CC-0 after counting PCI score.

### *Peritonectomy techniques to achieve CC-0 CRS for PC from gastric cancer*

The final goal of CRS is to remove all macroscopic PM, including primary tumor, the regional lymph nodes and PM, using peritonectomy technique[1,8,14]. Peritonectomy procedures include parietal and visceral peritonectomy. In parietal peritonectomy right and left subdiaphragmatic peritonectomy, pelvic peritonectomy, peritonectomy of right and left para-colic gutter and Morrison's pouch are removed. In visceral peritonectomy, multivisceral resection of small bowel, colon, rectum, spleen, gall bladder, uterus, vagina, lesser omentum, and omental bursa, are performed when they are involved. To remove primary tumor, total gastrectomy in combination with D2 lymph node dissection is usually done. Piso *et al*[21] reported that the incidences of postoperative morbidity and mortality after gastric resection and peritonectomy were acceptable even when combined with HIPEC.

For the skin incision, a generous midline skin incision starting at the xiphi-sternal junction above to symphysis pubis below is designed. If there is a scar of previous operation, it should be included in the skin incision. Ascites is then aspirated through a small window made on the peritoneum, and the ascites is studied for cytological examination. Before starting CRS, EIPL is done[17]. The peritoneal cavity is extensively shaken and washed after injection of 1 L of saline, and then the saline is completely aspirated. This procedure is repeated 10 times[17]. The rationale of EIPL is the removal of PFCCs from the peritoneal cavity by 10 times wash with 1 L of saline according to the "limiting dilution theory".

Parietal peritoneum is dissected off from the posterior sheath of rectus muscle (Figure 1). Then the dissection between diaphragm and peritoneum is done by ball-tip electrosurgery[14]. On the left upper quadrant, spleen and right subdiaphragmatic peritoneum are dissected from the anterior renal fascia, and the dissection plane reaches to the left side of celiac axis (Figures 2 and 3). Stomach is isolated from the attachment of lesser onentum to the Arantius' duct, and hepatoduodenal ligament by ligation of right gastric artery (Figure 4). On the right upper quadrant, complete stripping of the peritoneum covering subdiaphragmatic muscle, and the retroperitoneum covering on Morrison's pouch is dissected. Second portion of duodenum is identified and the anterior leaf of transverse mesocolon is removed with greater omentum (Figures 5 and 6). Then, 1$^{st}$ portion of the duodenum is cut at 1cm from pyloric ring. The proper hepatic artery and common hepatic artery are skeletonized by electro-surgical techniques. The left gastric artery and left coronary vein are cut at the roots. Esophagus is transected above the esophago-gastric junction, and the proximal margin of esophagus is sent to pathologic department to confirm the negative proximal surgical margin. Next, lymph nodes along splenic artery and splenic hilum are dissected and then splenic artery and

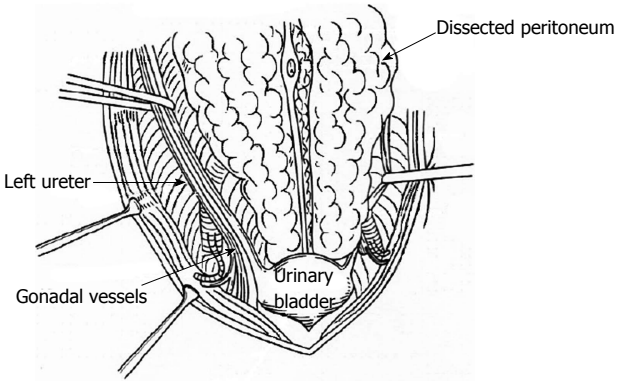


**Figure 1 Dissection of the lower parietal peritoneum.**

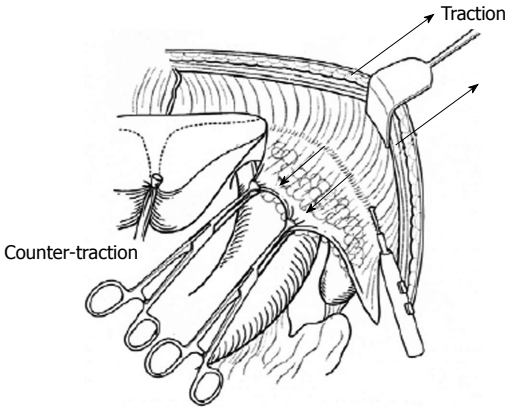


**Figure 2 Dissection of the upper right parietal peritoneum.**

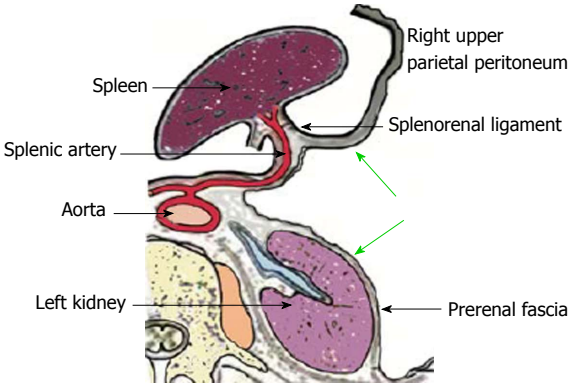


**Figure 3 Mobilization of spleen and pancreas tail.** The prerenal fascia is cut and the anterior surface of the left adrenal gland is visualized.

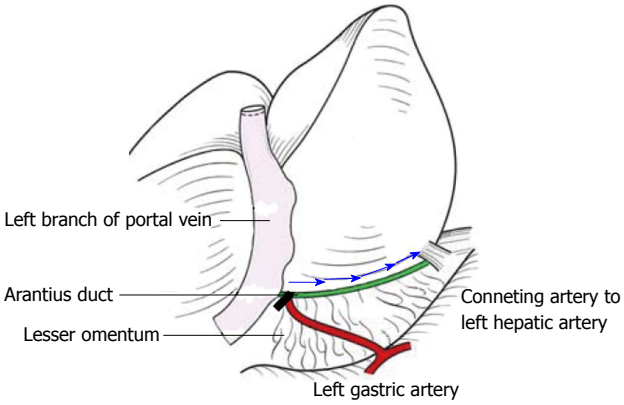


**Figure 4 Detachment of lesser omentum from Arantius' duct.**

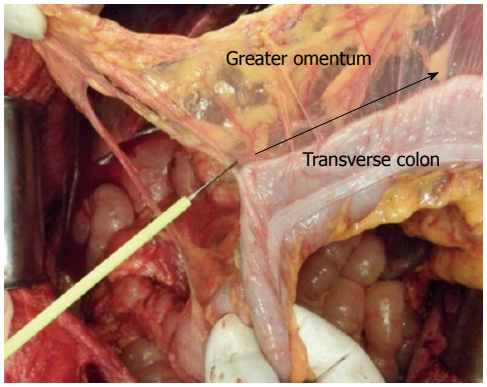


**Figure 5 Detachment of greater omentum from transverse colon.**

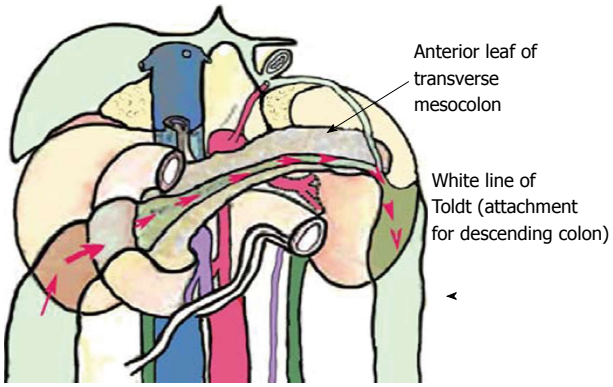


**Figure 6 Dissection plane between posterior and anterior transverse mosocolon.**

vein are cut at proximal part of their divergence.

Pelvic peritonectomy is started by stripping the peritoneum covering the urinary bladder. In male, anterior dissection plane reaches to the rectovesical pouch. In female, vagina is cut below the uterine cervix (Figure 7). After cutting and ligating the uterine vessels, vagina is transected with electric knife. Then, the posterior wall of vagina is dissected from the rectum. Rectum is freed from the pelvic structure. The posterior dissection reaches to the S4 presacral space by the preservation of pelvic nerve plexus and hypogastric nerve.

If the rectum is not involved, rectum-preserving pelvic peritonectomy is done (Figure 8).

When the rectum is involved, rectum is transected at 2 cm below cul-de-sac (Figure 9).

In terms of the treatment of ovarian metastasis from appendiceal mucinous neoplasm, Elias *et al*[22] proposed the preservation of ovaries in young women with appendiceal mucinous neoplasm for the childbearing, when the ovaries are macroscopically normal. Recurrence in the preserved ovary was found in 14% (3/21), and two women became pregnant after ovary-preserving peritonectomy. In patients with PM from gastric cancer,

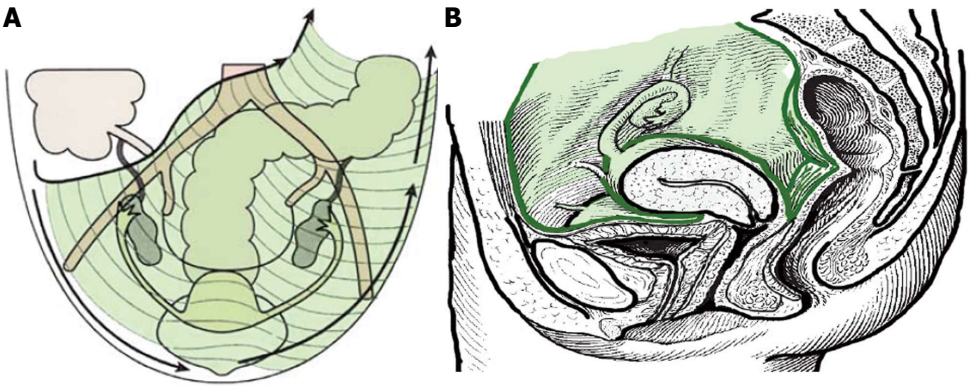


**Figure 7 Stripping of the pelvic peritoneum.** A: Stripping of the pelvic peritoneum from the urinary bladder and side walls of the pelvis in male; B: Stripping of the pelvic peritoneum with uterus and ovaries in female.

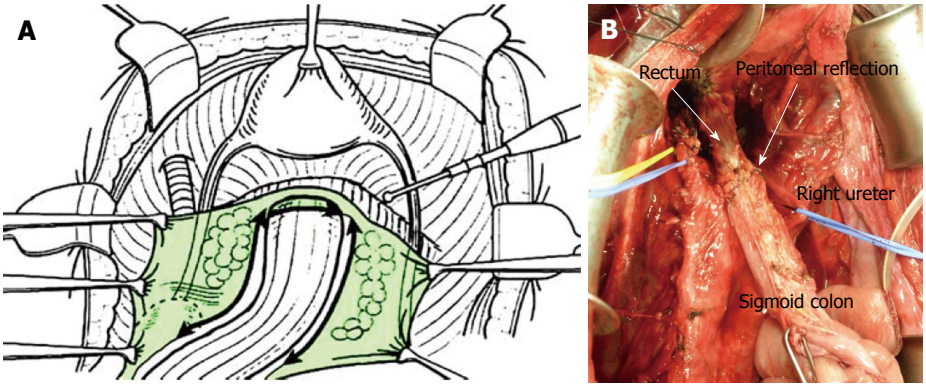


**Figure 8 Rectum-preserving peritonectomy.** A: The pelvic peritonectomy is started by stripping the peritoneum covering urinary bladder and recto-vesical pouch in male.and the dissection plane reaches the anterior wall of the rectum; B: Photograph after removal of pelvic peritoneum. Rectum is preserved completely.

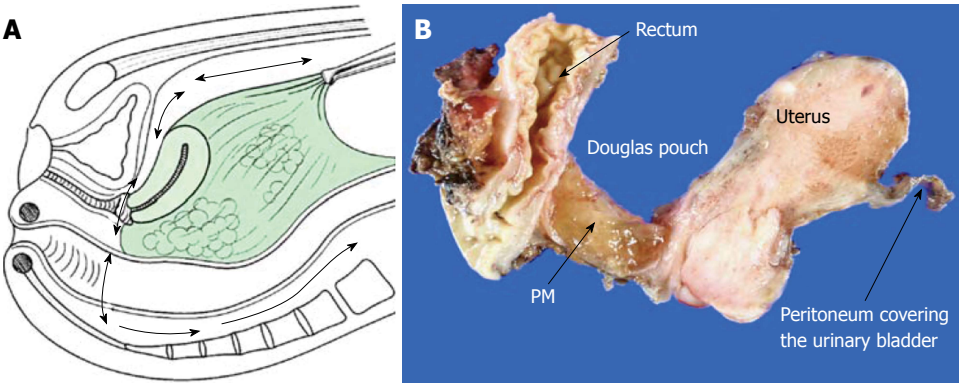


**Figure 9 Pelvic peritonectomy combined with the resection of rectum, uterus and vagina (A) and cut-section in a specimen of low anterior resection of rectum/hysterectomy/bilateral salphyngo-oophorectomy shows peritoneal metastasis on Douglas pouch (B).**

however, ovaries should be removed, because the incidences of ovarian and uterine involvement are higher than those from appendiceal mucinous neoplasms. In addition, the biological behavior of gastric cancer is more malignant than that of appendiceal mucinous neoplasms.

## NEOADJUVANT CHEMOTHERAPY

Complete cytoreduction is the strongest independent prognosticator[2-4]. However, survival of patients with PCI higher than the threshold value is poor, even if they received complete cytoreduction.

By the preoperative laparoscopic examination, Yonemura *et al*[23] reported that 21 (60%) of 35 patients without NAC showed the PCI score higher than the threshold level. Valle also reported that CC-0 can be achieved only in fewer than 30% of the cases who had not been treated with neoadjuvant chemotherapy (NAC)[24]. These results indicate that the patients with PCI higher than the threshold value diagnosed by

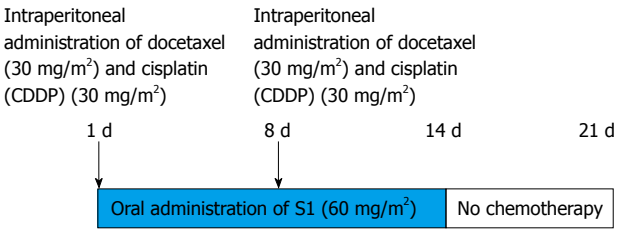


**Figure 10 Neoadjuvant intraperitoneal/systemic chemotherapy.** Oral S-1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) is administered for 14 d at a dose of 60 mg/m$^2$, following 7 d rest. Docetaxel (30 mg/m$^2$) and cisplatin (CDDP) (30 mg/m$^2$) are administered by intraperitoneal infusion on day 1 and days 8. Therapy is repeated three times, and laparptomy is done 3 to 4 wk after the last cycle.

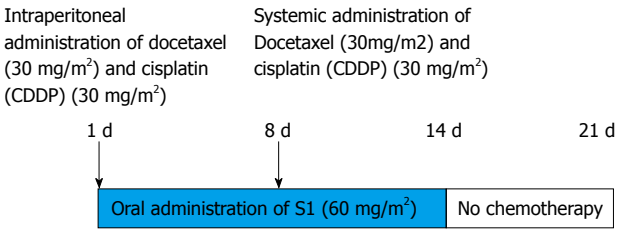


**Figure 11 Bidirectional intraperitoneal and systemic induction chemotherapy.** Oral S-1 is administered for 14 d at a dose of 60 mg/m$^2$, followed 7 d rest. Docetaxel (30 mg/m$^2$) and cisplatin (CDDP) (30 mg/m$^2$) are administered by intraperitoneal infusion on day 1, and the same dose of docetaxel and CDDP are systemically administered on days 8. Therapy is repeated three times, and laparotomy is done 3 to 4 wk after the last cycle.

**Table 1 Peritoneal wash cytology before and after bidirectional intraperitoneal and systemic induction chemotherapy**

| Cytology | Cytology after BIPSC | | |
|---|---|---|---|
| Before BIPSC | Negative | Positive | Total |
| Negative | 15 | 0 | 15 |
| Positive | 26 (79%) | 7 | 33 |
| | 41 | 7 | 48 |

Peritoneal wash cytology was done through a peritoneal port system after intraperitoneal administration of 500 mL of saline. BIPSC: Bidirectional intraperitoneal and systemic induction chemotherapy.

**Table 2 Peritoneal wash cytology before and after neoadjuvant intraperitoneal/systemic chemotherapy**

| Cytology | Cytology after NIPS | | |
|---|---|---|---|
| Before NIPS | Negative | Positive | Total |
| Negative | 47 | 1 | 48 |
| Positive | 69 (70%) | 30 | 99 |
| | 116 | 31 | 147 |

NIPS: Neoadjuvant intraperitoneal/systemic chemotherapy.

preoperative laparoscopy should be treated by NAC to reduce PCI less than the threshold level for good prognosis before CRS.

The aims of NAC are to achieve stage reduction to eradicate micrometastasis and PFCCs in the peritoneal cavity, and to improve the incidence of complete cytoreductiom.

Although systemic chemotherapy is still the standard treatment option for NAC[23,25,26], the response rates for PM after systemic chemotherapy were reported to be very low[23,26]. After systemic chemotherapy, treatment failure as a result of toxicity was also reported[26-29]. The reason why systemic chemotherapy does not work on PM is considered the existence of a blood-peritoneal barrier (BPB). BPB is a barrier consisting of stromal tissue between mesothelial cells and submesothelial blood capillaries[30]. BPB hinders the penetrating of drugs from systemic circulation into the peritoneal cavity. Accordingly, significantly larger amount of the drugs administered by systemic chemotherapy moves to the vital organs other than the peritoneum, resulting in the development of adverse effects.

In contrast, intraperitoneal (IP) chemotherapy generates a higher locoregional intensity of drugs in the peritoneal cavity than systemic chemotherapy[31,32]. During IP chemotherapy, the area under the curve (AUC) ratios of IP *vs* plasma exposure (PE) become high. Significant high AUC IP/PE ratios were found after the IP administration of paclitaxel, docetaxel, gemcitabine, 5-fluorouracil and doxorubicin[32]. The intraperitoneal concentrations of these drugs maintain long time because the molecular weights of these drugs are high.

In IP chemotherapy, penetration distance varies from drug to drug and drugs with a high penetration activity into the PM nodules should be selected. In the experimental PM, cisplatin penetrate approximate 2 mm from the surface of PM[31,32].

Recently, a combination chemotherapy of IP administration of cisplatin and docetaxel in combination with the oral administration of S-1 was developed and this method is designated NIPS (Figure 10)[28]. Yonemura *et al*[33] reported that PFCCs were eradicated by NIPS in 69% of patients with positive cytology before NIPS. Histologic examination of the resected specimens of PM after NIPS showed a complete histologic response rate of 37%. In addition, down staging was experienced in 15% of patients[33], and the survival of histological responder after CRS was significantly better than that of non responders. Accordingly, NIPS improves the complete cytoreduction rates, resulting in the long term survival after NIPS plus CRS.

More recently, a new regimen consisting of alternate administration of systemic and intraperitoneal chemotherapy was proposed. This method is called BISIC. By the alternate administration of systemic and IP chemotherapy, a wider treatment area can be treated than IP administration alone. Yonemura *et al*[34] reported a new method of BISIC. Oral S-1 is administered for 14 d at a dose of 60 mg/m$^2$ per day, followed by 7 d rest. Docetaxel (30 mg/m$^2$) and cisplatin (CDDP, 30 mg/m$^2$) are administered by IP infusion on day 1, and the same dose of docetaxel and CDDP are administered intravenously on day 8 (Figure 11). Therapy is repeated three times, and laparotomy is done two weeks after the last administration of S-1 (Figure 10). As shown in Table 1, 79% of patients with positive cytology before BISIC

**Table 3 Histoloogic effects of primary tumor and peritoneal carcinomatosis in 41 patients after bidirectional intraperitoneal and systemic induction chemotherapy**

| | EF-0 | EF-1 | EF-2 | EF-3 | Total |
|---|---|---|---|---|---|
| Primary tumors | 3 (12%) | 15 (58%) | 7 (27%) | 1 (4%) | 26 (100%) |
| Peritoneal metastasis | 7 (17%) | 18 (44%) | 7 (17%) | 9 (22%) | 41 (100%) |

EF-0: No histological change or histologic change is found in less than one-third of the tumor tissue; EF-1: Degeneration of cancer cells is detected in the tumor tissue ranging from one-third to less than two thirds; EF-2: The degeneration of cancer cells is found in more than two-thirds of the tumor tissue; EF-3: Complete disappearance of cancer cells.

**Table 4 Histoloogic effects of primary tumor and peritoneal carcinomatosis in 147 patients with PC treated with neoadjuvant intraperitoneal/systemic chemotherapy**

| | EF-0 | EF-1 | EF-2 | EF-3 | Total |
|---|---|---|---|---|---|
| Primary tumors | 13 (18%) | 38 (54%) | 20 (28%) | 0 | 71 (100%) |
| Peritoneal metastasis | 59 (40%) | 35 (24%) | 14 (10%) | 39 (25%) | 147 (100%) |

**Table 5 Side effects during bidirectional intraperitoneal and systemic induction chemotherapy**

| Grade 0 | Grade 1-2 | Grade 3 | Grade 4 | Grade 5 | Total |
|---|---|---|---|---|---|
| 44 (76%) | 8 (14%) | 4 (7%) | 2 (3%) | 0 (0%) | 58 |

Experienced grade 3 side effects were meningitis in 1, ileus in 1 and bone marrow suppression in 2 patients. Grade 4 side effects of diarrhea and port infection were experienced in two patients.

became negative cytology after 3 cycles of BISIC (Table 1). Table 2 shows the changes of the cytologic status before and after NIPS. After NIPS, 70% of patients with positive cytology before NIPS became negative cytology. Histologic response rates in PC after BISIC and NIPS were 83% (34/41) and 60% (88/147), respectively (Tables 3 and 4). There was a statistical significance in histologic response rate between BISIC and NIPS. Complete pathologic response on primary tumor and PM were found in 4%, (1/26), and 22% (9/41) of patients treated with BISIC (Table 3).

Ishigami *et al*[35] reported a new BISIC method using systemic and IP paclitaxel (PTX) combined with S-1. The overall response rate was 56%, and one-year overall survival rate was 78%.

A systemic review and meta-analysis, IP chemotherapy combined with CRS is associated with significant improved overall survival[36].

From these results, NIPS and BISIC are effective treatments to eradicate PFCCs and to reduce PCI before CRS.

Yonemura *et al*[34] reported that the incidences of major complications (grade 3, 4, and 5) during NIPS and BISIC were 10.4% and 9.9%[35-37] (Table 5). These values are similar to the major complication rates after systemic chemotherapies[28,38], and are considered to be acceptable.

Although NIPS/BIPSC may improve the incidence of complete cytoreduction at CRS, NIPS might increase the morbidity and mortality after CRS. Yonemura *et al*[38] reported that the hospital death occurred in 3.7% of patients after NIPS plus CRS, and postoperative major complications occurred in 24.4% of patients. Reoperation was done in 7.6% (6/79) of patients. Glehen *et al*[7] reported a mortality rate of 4%, and a major complication rate of 27%. The magnitude of surgery, number of resected organs and anastomoses, and the operation time contribute to the development of complication after CRS plus HIPEC. To avoid futile CRS, the patients for the candidate of CRS should be strictly selected. For the selection of patients, preoperative PCI assessment by laparoscopy is important.

## ROLES OF LAPAROSCOPY

There are limitations to estimate the precise PCI by CT, magnetic resonance imaging and positron emission tomography[10]. The sensitivity of the diagnosis for the PM smaller than 10 mm in diameter by CT is reported to be only 8%[10].

To improve the preoperative correct diagnosis of PCI and to select the patients for CRS, staging laparoscopy was introduced[39]. Laparoscopy enables to know the histological and cytological diagnosis and to evaluate the effects of NAC. In addition, LHIPEC just after the laparoscopic diagnosis of PM was developed[39]. Very high response on ascites by LHIPEC was reported[39]. Penetration distance of drugs into the PM in LHIPEC (closed HIPEC) is longer than that in open HIPEC performed under the laparotomy, because the intraperitoneal pressure in closed HIPEC is significantly higher than that in the open HIPEC[40].

So far, no evidence was reported about the direct effects on PM by HIPEC. Yonemura *et al*[23] first reported a direct effect of HIPEC on PM from gastric cancer. Two cycles of diagnostic laparoscopy and LHIPEC with an interval of one month were done for 50 gastric cancer patients with PM. Ascites completely disappeared or decreased in 64.7% (22/34) of patients and 20 patients with positive peritoneal cytology at the 1st LHIPEC became negative cytology in 14 (70%) patients at the 2nd LHIPEC. Six (12%) patients showed complete disappearance of PM and PCI was significantly reduced from 14.3 ± 10.2 at the 1st LHIPEC to 10.8 ± 10.5 at the 2nd LHIPEC ($P < 0.05$). Furthermore, total PCI scores (6.56 ± 2.92) on small bowel mesentery (BS-PCI) at 1st HIPEC were significantly decreased at 2nd LHIPEC (5.25 ± 3.78) ($P = 0.016$). LHIPEC reduces the SB-PCI before CRS, and the incidence of complete cytoreduction may improve.

Diagnostic laparoscopy is a convenient method to select patients for CRS and neoadjuvant LHIPEC is an effective therapy for the control of ascites and for the eradication of PFCCs. Furthermore, PCI levels can be reduced by LHIPEC and LHIPEC increase the number of patients who will undergo complete CRS. Accordingly,

LHIPEC is recommended to perform as a neoadjuvant induction treatment before CRS.

## MECHANISMS OF HIPEC

The first report of CRS and HIPEC in a patient with PC from gastric cancer dates back to 1980s[41-43]. Since then, CRS and HIPEC have been performed to treat for this group of patients. However, there has been only one prospective randomized trial[43]. From the literatures, benefit of the HIPEC is to eradicate micrometastasis left after complete cytoreductio[35,44].

In many institutes, HIPEC is usually performed at the temperature of lower than 42 ℃ for 90 min.

Heat lower than 42 ℃ (mild hyperthermia) can not eradicate cancer cells by the thermal tolerance *via* the upregulation of heat shock protein[45]. Heat shock protein repair degenerated protein by mild hyperthermia, and cancer cells survive. Even in the mild hyperthermia, however, the fraction of hypoxic cells locate apart from vasculature are killed and thus cellular acidity increase thermal sensitivity *in vivo*. Generally, a temperature of Arrhenius "break" temperature of 43 ℃ and treatment time of at least 30 min are recommended. In United States and European institutes, mild hyperthermia of 41 ℃-42 ℃ for 60 to 90 min. is carried out[7,21,24]. In Japan, 43 ℃ to 43.5 ℃ for 30 min. is a standard thermal dose of HIPEC[8]. Thermal dose is a treatment unit provided by the temperature and exposure time during hyperthermia.

Cells are killed according to the exponential manner if the temperature is higher than 43 ℃ *in vivo*. The cytocidal effects by the 43 ℃ hyperthermia are equivalent to those by 42 ℃ hyperthermia for three- to four-fold longer treatment time than by 43 ℃ hyperthermia. Namely, to obtain the same cytocidal effect by 43 ℃ for 30 min requires 90 to 120 min by 42 ℃ hyperthermia[46].

Hyperthermia enhances the cytotoxic effects of some anti-cancer drugs. Melphalan, mitomycin C, cisplatin, docetaxel, gencitabine, and irinotecan[47-50] enhance cytotoxicity when combined with hyperthermia. In HIPEC for gastric cancer, direct cytotoxic agents like mitomycin C, cisplatin and docetaxel are used[33,41,51].

Pharmacokinetic studies revealed that approximately 70% of mitomycin C is absorbed from the perfusate after 2 h HIPEC[52]. In cisplatin, 75% is eliminated from the perfuate after 90 min HIPEC, but only 20% of the cisplatin moves to the systemic circulation[53]. Accordingly, 50% of ciplatinum is absorbed in the PM nodules and peritoneal tissue during 90 min of HIPEC.

In the case of docetaxel, 40% is adsorbed during 40 min HIPEC at 43 ℃-43.5 ℃[51].

Temperature higher than 39 ℃ increases drug penetration distance[54]. The drug penetration into the peritoneal nodules is limited, because stromal pressure in PM is higher than that in normal tissue[54]. Carboplatin and cisplatin penetrate 1-2 mm from the peritoneal surface during intraperitoneal perfusion without hyperthermia, but penetration distance increases up to 2-3 mm when hyperthermia is combined[31]. Penetration depth from the peritoneal surface depends on the treatment time. Membrane permeation index (Paap) is the penetration distance of the drugs from peritoneal surface per minute, and is calculated by the following equation; Papp (cm/h) = CLp (drug clearance from peritoneal cavity, mL/h)/peritoneal surface area ($cm^2$). From this equation, Papp after 40 min. HIPEC using 40 mg of docetaxel was 1.5 mm/40 min[51]. If the tumors larger than 1.5 mm in diameter are treated by HIPEC with docetaxel, treatment time should be prolonged to increase the penetration distance of drugs.

However, HIPEC increases the operation time and may cause morbidity. A meta-analysis did not show a significant difference in the mortality rates between HIPEC and control group[44]. However, a significant increase was found in the incidence of abdominal abscess and neutropenia after HIPEC.

A randomized control study for colorectal carcinomatosis revealed significant better survival of CRS plus HIPEC group than that of traditional systemic chemotherapy plus CRS group[55].

At present, combination of CRS plus HIPEC is the standard of care recommended for PM from appendiceal mucinous neoplasm and diffuse malignant peritoneal mesothelioma[56].

Before 2011, there was no randomized control study to confirm the effect of HIPEC on survival of gastric cancer patients with PM. Yang *et al*[43] first reported the efficacy of HIPEC on survival by phase Ⅲ randomized clinical trial. They reported that CRS + HIPEC with mitomycin C 30 mg and cisplatin 120 mg improved the survival with acceptable morbidity. Further phase Ⅲ trials should be done to confirm the effects of HIPEC on PM from gastric cancer.

## INDICATION OF THE COMPREHENSIVE TREATMENT

A multivariate analysis using Cox proportional hazard model revealed that CC score, PCI threshold, histologic effect after NAC, cytologic status and HIPEC were independent prognostic factors (Table 6)[7,8]. Among these prognostic factors, PCI threshold level after NAC is the strongest prognostic factor. Survival of patients who received incomplete CRS after NIPS was similar to that of patients treated with NIPS alone (Figure 12). Accordingly, patients who are diagnosed as receiving incomplete CRS by laparoscopy should be excluded from the candidates for CRS.

Survival of histological responders after NAC with negative cytology and PCI ≤ 6 after complete CRS and HIPEC is shown in Figure 13. Five-year survival rate was 32.4%.

## CONCLUSION

Patients with PM from gastric cancer are recommended to treat with NIPS or BISIC before CRS. Indication

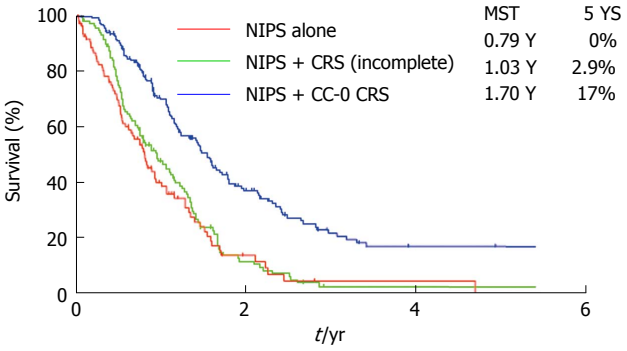


**Figure 12 Survival curves of patients treated with cytoreductive surgery and neoadjuvant intraperitoneal/systemic chemotherapy alone.** CRS: Cytoreductive surgery; NIPS: Neoadjuvant intraperitoneal/systemic chemotherapy.

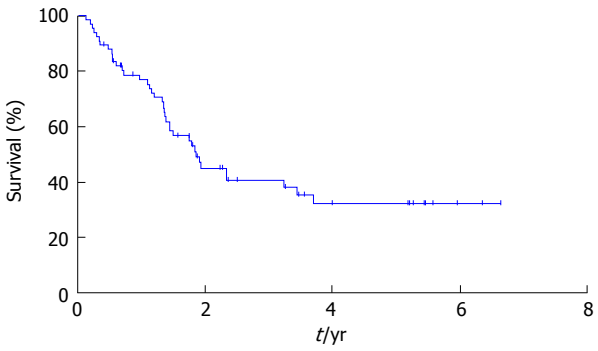


**Figure 13 Survival of histological responders with negative cytology and peritoneal cancer index ⩽ 6 after complete cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy.**

**Table 6 Multivariate analysis of 304 patients with peritoneal metastasis treated with a comprehensive treatmnent**

| Prognostic factors | $\chi^2$ | *P* value | HR | 95%CI | |
|---|---|---|---|---|---|
| Sex male *vs* female | 0.263 | 0.60752 | 0.9218 | 0.676 | 1.257 |
| CC score: complete *vs* incomplete | 4.03 | 0.04468 | 1.504 | 1.01 | 2.24 |
| Nodal involvement: N0-1 *vs* N2-3 | 0.445 | 0.50454 | 1.1338 | 0.784 | 1.639 |
| Neoadjuvant chemo.: negative *vs* positive | 2.517 | 0.11259 | 1.3445 | 0.933 | 1.938 |
| PCI: ⩽ 6 *vs* ⩾ 7 | 8.809 | 0.00299 | 1.7863 | 1.218 | 2.621 |
| HIPEC: Not done *vs* done | 8.218 | 0.00414 | 0.6322 | 0.462 | 0.865 |
| Histilogicl effects: EF 0-1 *vs* EF 2-3 | 12.305 | 0.00045 | 0.469 | 0.307 | 0.716 |
| Cytology: Negative *vs* positive | 8.2163 | 0.00415 | 1.8458 | 1.213 | 2.806 |

PCI: Peritoneal carcinomatosis index; HIPEC: Hyperthermic intraoperative intraperitoneal chemotherapy.

of CRS should be determined by laparoscopy. The best indications of the comprehensive treatment are patients with PCI levels within threshold level, and responders after NAC. Patients who satisfy these factors should undergo gastrectomy combined with D2 lymph node dissection and complete removal of PM using peritonectomy techniques. Just after complete cytoreduction, HIPEC should be done[35].

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